Citation:

Godwin KA, Sibbald B, Bedard T, Kuzeljevic B, Lowry RB, Arbour L. Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry. *Canadian Journal of Public Health.* 2008; 99: 271-275.

PubMed ID: 18767269

Study Design:

Trend Study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To use the Canada-based Alberta Congenital Anomalies Surveillance System (ACASS) to examine changes in birth prevalence of select structural congenital anomalies between pre- and post-folic acid fortification of grain products (1992 to 1996 vs. 1999 to 2003).

Inclusion Criteria:

- Live birth or stillbirth in the province of Alberta, Canada between 1992 to 1996 or 1999 to 2003
- One or more congenital anomaly diagnosed up to one year of age, including anencephaly, spina bifida, cleft palate, cleft lip, obstructive defects of the renal pelvis and ureter, reduction deformities of the upper or lower limb, bulbus cordis anomalies and anomalies of cardiac septal closure, common truncus, transposition of great vessels, tetralogy of Fallot, ventricular septal defect, ostium secundum type atrial septal defect, anomalies of the abdominal wall, omphalocele, gastroschisis or hypertrophic pyloric stenosis
- Neither informed consent processes nor IRB review were mentioned in the article.

Exclusion Criteria:

- Live birth or stillbirth prior to 1992, between 1997 and 1998 or after 2003
- Aborted pregnancy.

Description of Study Protocol:

Recruitment

- All live births and stillbirths in Alberta, Canada during the target periods were recorded in the Alberta Congenital Anomalies Surveillance System (ACASS)

- Infants diagnosed with a congenital anomaly at birth, hospital admission or death had a notification form completed and submitted to ACASS by trained hospital personnel.

Design

- The surveillance system relied on vital records to ascertain live births and stillbirths
- As a trend design, the study compared frequencies of congenital anomalies pre- and post-folic acid fortification of grain products
- Infants with one or more anomaly were counted in multiple categories.

Statistical Analysis

- The number of live births and stillbirths constituted the denominator for each time period. The numerator was both the individual number of each congenital anomaly, but also the total number of anomalies for each time period
- Odds ratios were determined using the chi-square approximation
- The Bonferroni correction was applied to adjust for multiple testing, so a P-value of less than 0.003 was required for statistical significance.

Data Collection Summary:

Timing of Measurements

Ascertainment of a congenital anomaly could occur up to one year after birth. How diagnoses were determined was not described.

Dependent Variables

Folic acid-linked congenital anomalies, including anencephaly, spina bifida, cleft palate, cleft lip, obstructive defects of the renal pelvis and ureter, reduction deformities of the upper or lower limb, bulbus cordis anomalies and anomalies of cardiac septal closure, common truncus, transposition of great vessels, tetralogy of Fallot, ventricular septal defect, ostium secundum type atrial septal defect, anomalies of the abdominal wall, omphalocele, gastroschisis or hypertrophic pyloric stenosis.

Independent Variables

Pre-folic acid fortification (1992 to 1996) vs. post-folic acid fortification (1999 to 2003) of grain products.

Description of Actual Data Sample:

- *Initial N:* 389,349
    - 198,321 in 1992 to 1996
    - 191,028 in 1999 to 2003
- *Location:* Alberta, Canada.

Summary of Results:

- From pre- to post-fortification, there were significant decreases in birth prevalence of spina bifida and ostium secundum type atrial septal defects. Prevalence also decreased for

anencephaly, cleft lip, cleft lip and palate, bulbus cordis anomalies and anomalies of caridac septal closure, common truncus and tetralogy of fallot, but not significantly

- Prevalence increased significantly for obstructive defects of the renal pelvis and ureter, anomalies of the abdominal wall, gastroschisis and hypertrophic pyloric stenosis. Non-significant increases were observed for cleft palate, reduction limb deformities, transposition of the great vessels and omphalocele.

Congenital Anomaly	Pre-fortification (1992 to 1996) N=198,321		Post-fortification (1999 to 2003) N=191,028		OR	95% CI	P-value
	N	Per 1,000 Births	N	Per 1,000 Births			
Anencephaly	38	0.19	27	0.14	0.74	0.45 to 1.21	0.2759
Spina bifida	**97**	**0.49**	**48**	**0.25**	**0.51**	**0.36 to 0.73**	**0.0002**
Cleft palate	146	0.74	159	0.83	1.12	0.90 to 1.42	0.3102
Cleft lip	84	0.42	75	0.39	0.93	0.68 to 1.27	0.6924
Cleft palate and cleft lip	155	0.78	140	0.73	0.94	9.75 to 1.18	0.6215
Obstructive defects of the renal pelvis and ureter	**267**	**1.35**	**373**	**1.95**	**1.45**	**1.24 to 1.70**	**<0.0001**
Reduction deformities of the upper limb	121	0.61	127	0.66	1.10	0.85 to 1.40	0.5400
Reduction deformities of the lower limb	63	0.32	72	0.38	1.19	0.85 to 1.64	0.3647
Bulbus cordis anomalies plus anomalies of cardiac septal closure	1,183	6.00	1,107	5.80	0.97	0.89 to 1.06	0.5009
Common truncus	14	0.07	10	0.05	0.74	0.33 to 1.67	0.6026
Transposition of great vessels	64	0.32	72	0.38	1.17	0.83 to 1.64	0.4128
Tetralogy of Fallot	63	0.32	56	0.29	0.92	0.64 to 1.32	0.7295
Ventricular septal defect	536	2.70	528	2.76	1.02	0.91 to 1.15	0.7372
Ostium secundum type atrial septal defect	**412**	**2.10**	**319**	**1.70**	**0.80**	**0.69 to 0.93**	**0.0037**

Anomalies of the abdominal wall	**77**	**0.39**	**104**	**0.54**	**1.40**	**1.04 to 1.88**	**0.0289**
Omphalocele	30	0.15	43	0.23	1.49	0.03 to 2.37	0.1176
Gastroschisis	**38**	**0.19**	**70**	**0.37**	**1.91**	**1.29 to 2.84**	**0.0015**
Hypertrophic pyloric stenosis	**119**	**0.60**	**171**	**0.90**	**1.49**	**1.18 to 1.89**	**0.0009**
Total	3,507	18.00	3,501	18.00	1.02	0.99 to 1.00	0.1300

Author Conclusion:

- This provincial registry-based analysis supports previously recognized reductions in spina bifida and anencephaly attributable to folic acid fortification
- The fact that there was no overall increase in septal defects and a significant reduction in atrial septal defects was observed may support the hypothesis that folic acid is at least one of the critical nutrients responsible for the reduction in heart defects associated with multivitamin use
- Gastroschisis, a defect presumably caused by vascular disruption, is increasing, especially in younger women. The rising rate seems to pre-date folic acid fortification, and likely reflects a pre-existing, unrelated trend.
- Even after folic acid awareness campaigns, fewer than 50% of women take folic acid-containing multi-vitamins. Thus, fortified grain products remain an important source of folic acid for the majority of women.

Reviewer Comments:

- *The authors identified the following limitations:*
  - *A registry analysis can only reveal associations between the timing of fortification and trends in birth defects rates*
  - *Since elective abortion data were not recorded in the pre-fortification time period, they could not be used in the analyses*
  - *Changing demographics were not assessed; demographic shifts between the time periods may account for the increasing prevalence observed with some of the anomalies*
- *The association between the observed trends and folic acid fortification must be considered carefully. Individuals' folate and folic acid intake were not measured, so ecological observations should not be applied to individuals within the population*
- *Although the article notes that hospital personnel reporting congenital anomalies to ACASS were trained and supervised, it is unclear whether anomalies were reported consistently across hospitals in the province (including both case identification as well as any potential non-response issues). Any differences in consistency between hospitals and overtime may confound the study findings.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	???
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	No
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	???

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes